PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
1178WOORD01		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/050428	02.04.2004	04.04.2003

International Patent Classification (IPC) or national classification and IPC
C07D471/04, C07D491/04, A61K31/4188, A61K31/437, A61P1/04

Applicant
ALTANA PHARMA AG et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the International application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.10.2004	23.02.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050428

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4).
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-57 as originally filed

   Claims, Numbers

   1-12 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050428

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. **Re Item I *(Basis of the report)***

Reference is made to the following documents:

D1: WO 97/47603 A (DAHLSTROEM MIKAEL ; AMIN KOSRAT (SE); ASTRA AB (SE); NORDBERG PETER (S) 18 December 1997 (1997-12-18)

D2: KAMINSKI J J ET AL: "ANTIULCER AGENTS. 5. INHIBITION OF GASTRIC H+/K+-ATPASE BY SUBSITUTED IMIDAZOL1,2-A PYRIDINES AND RELATED ANALOGUES AND ITS IMPLICATION IN MODELING THE HIGH AFFINITY POTASSIUM ION BINDING SITE OF THE GASTRIC PROTON PUMP ENZYME" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, 1991, pages 533-541, XP000919185 ISSN: 0022-2623

D3: KAMINSKI J J ET AL: "ANTIULCER AGENTS. 6. ANALYSIS OF THE IN VITRO BIOCHEMICAL AND IN VIVO GASTRIC ANTISECRETORY ACTIVITY OF SUBSTITUTE IMIDAZO1,2-A PYRIDINES AND RELATED ANALOGUES USING COMPARATIVE MOLECULAR FIELD ANALYSIS AND HYPOTHETICAL ACTIVE SITE LATTICE METHODOLOGIES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 40, 1997, pages 427-436, XP000941533 ISSN: 0022-2623

D4: WO 03/014123 A (BUHR WILM ; ALTANA PHARMA AG (DE); SENN-BILFINGER JOERG (DE)) 20 February 2003 (2003-02-20)

D5: EP-A-0 266 326 (HAESSLE AB) 4 May 1988 (1988-05-04)

2. **Re Item V *(Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement)***

2.1 Subject-matter

The present application relates to tricyclic benzimidazoles of formula I (chromeno[7,8-a]imidazoles or imidazol[4,5-h]quinolines) useful in the treatment of gastrointestinal diseases due to their gastric acid secretion inhibitory activity.

2.2 Novelty

The present application differs from

- documents D1 and D2 in view of the present tricyclic core structure of formula

(I)

- documents D2-D4 in view of the present benzimidazole part

The requirements of novelty are presently considered as fulfilled.

2.3 Inventive step

Document D1 is presently considered as **closest prior art**. This document discloses bicyclic benzimidazole derivatives, wherein the benzimidazole moiety is substituted e.g. at position 4 with a benzyloxy- or benzylamino-group (see compounds A and B on pages 23-24). The compounds disclosed in D1 inhibit the gastric acid secretion (see biological tests on pages 22-27) and are useful for the treatment of gastrointestinal diseases (see claims 20 and 21).

In view of this document, the **problem to be solved** can be regarded as the provision of further compounds having the same activity as those of document D1.

The **solution** consists in compounds of present formula (I) characterized by a tricyclic core moiety.

In view of the data on page 21, the problem is considered as being solved at least for the exemplified compounds.

However, the proposed solution is presently considered as obvious in the light of document D1 in combination with documents D2-D4.

The compounds of present formula (I) are considered as rigid analogues of the compounds of document D1, wherein the benzyloxy- or benzylamino-group (see D1, compounds A and B on pages 23-24) is fixed in an additional third cycle.

Such analogisations are well known to a person skilled in the art as demonstrated e.g. by the teaching of documents D2 and D3. These documents disclose the identical rigid analogisation (see introductory part of D5 and D6) for another well known inhibitor of gastric acid secretion, the imidazo[1,2-a]pyridine 'Sch 28080' (see D5, table 1, compounds 1 and 4; see also D6, table 1, compounds 1 and 15).

Accordingly, the provision of rigid analogues starting from document D1 and

taking into account the technical teaching of documents D2 and D3 is merely one of several straightforward possibilities from which the skilled person would select, without any exercise of inventive skill, in order to solve the problem defined above.

Furthermore, starting from document D4 disclosing tricyclic imidazopyridines, the presently claimed subject-matter appears to be obvious, too. The compounds of the present formula (I) appear to represent a mere bioisoteric analogisation of the compounds of document D4. Moreover, underlying the principles of structure-activity relationship (SAR), it is stressed that for structural similar compounds a similar biological activity can be expected. As a consequence thereof, SAR allow to predict that for formal analogisations the pharmaceutical activity will be maintained. Therefore, the analogisation of the tricyclic core starting from document D4 is merely one of several straightforward possibilities from which the skilled person would select, without any exercise of inventive skill, in order to solve the problem defined above.

Accordingly, the presently claimed subject-matter does not fulfill the requirements of inventive step.

However, SAR does not allow the prediction as to whether the quantitative biological activity for structurally similar compounds is better or worse. As a consequence thereof, an unexpected effect can be considered as an indication for inventive step. However, the Applicant has not yet shown, that the claimed compounds are likely to have such an unexpected effect compared to those described in the prior art, in particular the nearest possible compounds, which are represented by document D1, compounds (A) and (B) (see section "Biological Data").

In view of the scope of claim 1, the attention of the applicant is drawn to the point, that substantially all embodiments covered by the claims should satisfy the criteria of inventive step. When the inventive step is solely based on the achievement of a beneficial effect, substantially all embodiments should exhibit this effect. The Applicant is invited to submit all information available to him to substantiate that all claimed compounds represent a solution to the problem underlying this application according Art. 56 or - if necessary - to restrict the claims to such compounds which illustrate patentable effects.